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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Masahiko KOIKE et al.
Title:	SOLID PREPARATION
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DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam/Sir:

1. I, Masahiko Koike, the undersigned, a citizen of Japan residing at 2-2-29, Senrien, Toyonaka-shi, Osaka 560-0046, JAPAN, do hereby declare:

2. I graduated from Toyama Medical and Pharmaceutical University with a degree of Master of Science in March 1991, and I was a visiting scientist in the Department of Industrial and Physical Pharmacy at Purdue University from April 2005 to March 2006.

3. I have been employed by Takeda Pharmaceutical Company Limited, Osaka, Japan, the Assignee of the present application, and have been engaged in pharmaceutical research therein since April 1991. I am not receiving any additional compensation for preparing this Declaration other than my normal compensation as an employee at Takeda Pharmaceutical Company Limited.

4. I am one of the co-inventors of the present patent application. I have reviewed and am familiar with the October 15, 2009 Office Action and the references cited therein. I hereby submit this Declaration to supplement the Declaration submitted on July 24, 2009. I remain of the opinion that the presently claimed invention is patentable over the prior art, particularly in view of the unexpected desirable properties resulting from the invention described below. The experimental results described below were obtained by either myself or another under my supervision.

Unexpected success provided by present invention

5. At the outset, the July 24, 2009 Declaration was not based only on an opinion but was based on the results of the experiments conducted according to the Paddle method, as described on pp. 2-3 of the Declaration, which also references the present Specification.

6. As provided in the July 24, 2009 Declaration, discrepancies between *in vitro* and clinical studies of a combination drug, which contained pioglitazone (pioglitazone hydrochloride) and metformin (metformin hydrochloride) as active ingredients, were observed when a median size of pioglitazone tested was above the micronized range (i.e., 2-10 μm). Specifically, when a combination drug with pioglitazone of a median size of 13 μm was administered to a human and the blood concentration profiles of these active ingredients were examined during *in vivo* clinical studies, the pioglitazone in the combination drug was not found to be bioequivalent to that in a drug ("Actos®") with pioglitazone as the single active ingredient. By contrast, during clinical studies, metformin in the combination drug was found to be bioequivalent to that in a drug ("Glucophage®") with metformin as the single active ingredient. The results of the bioequivalence determination are provided in Table DD1, and a summary thereof is provided in Table DD2. Note Table DD2 is the same as Table D1 presented in the July 24, 2009 Declaration and is provided herein again to facilitate the comparison and contrast.

Table DD1. Results of clinical studies demonstrating that bioequivalence of pioglitazone was not established when the particle size of pioglitazone was not "micronized" (i.e., 2-10 μm).

Clinical results of monolayer FDC (US, n=68)

"Non-micronized Pioglitazone used"

Formulation	FDC Non-micronized Pioglitazone used 15mg+500mg	Coadministered Actos® 15mg	Coadministered Glucophage® 500mg
Pioglitazone			
C_{max} (ng/mL)	577.8	690.9	-
AUC_{0-t} (h*ng/mL)	4591.3	5733.4	-
90% CI for Ratio (%)			
C_{max}	76.8-91.0 ← Not Bioequivalent		-
AUC_{0-t}	75.8-84.6		-
Metformin			
C_{max} (ng/mL)	1470.0	-	1427.6
AUC_{0-t} (h*ng/mL)	7170.8	-	7070.2
90% CI for Ratio (%)			
C_{max}	97.0-109.3 ← Bioequivalent		-
AUC_{0-t}	94.5-108.9		-

Acceptance range of the 90% CIs for the ratios: 80-125 %

Table DD2. Bioequivalence results of the two ingredients – pioglitazone and metformin as observed during *in vitro* dissolution test and clinical results.

Fixed Dose Combination (FDC)	*In vitro* Dissolution	Clinical Results
pioglitazone	Equivalent to Actos®	Not bioequivalent to Actos®
metformin	Not equivalent to Glucophage®	Bioequivalent to Glucophage®

7. These discrepancies can be eliminated, thereby achieving bioequivalence for both pioglitazone and metformin when the median particle size of pioglitazone in the present combination drug was reduced to between 2 and 10 μm ("micronized"). The results of the bioequivalence as established by the micronization of pioglitazone are provided in Table DD3. Even more surprisingly, it was observed that micronization of the pioglitazone had no significant effect upon the uniformity of both of the active pharmaceutical ingredients, as shown in Table DD4.

Table DD3. Results of clinical studies demonstrating that bioequivalence of pioglitazone was established when the particle size of pioglitazone was "micronized" (i.e., 2-10 μm).

Clinical results of micronized monolayer FDC (US, n=66)

Present invention

Formulation	FDC Micronized Pioglitazone used 15 mg + 500 mg	Coadministered Actos® 15mg	Coadministered Glucophage® 500mg
Pioglitazone			
C_{max} (ng/mL)	540.9	569.5	-
AUC_{0-t} (h*ng/mL)	4715.6	4827.1	-
90% CI for Ratio (%)			
C_{max}	86.2-104.7 ← Bioequivalent		-
AUC_{0-t}	91.0-104.9		-
Metformin			
C_{max} (ng/mL)	1160.1	-	1171.5
AUC_{0-t} (h*ng/mL)	7257.8	-	7073.4
90% CI for Ratio (%)			
C_{max}	94.8-103.4 ← Bioequivalent		-
AUC_{0-t}	97.9-107.5		-

Acceptance range of the 90% CIs for the ratios: 80-125 %

Table DD4. Non-micronized pioglitazone showed a fairly low variation level of the Active Pharmaceutical Ingredients (APIs), which level was comparable to that of the micronized pioglitazone. Therefore, micronization of pioglitazone had no significant effect upon the uniformity of both of the APIs.

Content uniformity of the APIs

	FDC "Non-Micronized Pioglitazone used"	**FDC "Micronized Pioglitazone used"** ***Present Invention***
Pioglitazone HCl		
Range (%)	96.4-100.9	98.1-101.8
RSD (%)	1.6	1.1
Metformin HCl		
Range (%)	97.6-99.7	99.5-102.2
RSD (%)	0.8	1.0

8. In sum, a median size of pioglitazone at 2-10 μm has enabled control of the blood concentration profile of a combination drug within a desired range, thereby achieving bioequivalence for both the pioglitazone and the metformin in the presently claimed combination drug. At the same time, reducing the particle size of pioglitazone to this range did not significantly affect the uniformity of either of the active pharmaceutical ingredients.

9. The ratio of the median size of metformin to that of the pioglitazone was held constant during the experiments above merely to illustrate the effect of micronization of the pioglitazone; but this should not be construed as an indication that the ratio is unimportant.

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10. I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of

Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 12th day of March, 2010.

Masahiko Koike

Masahiko Koike